



# Clinical Outcome Assessment (COA) Implementation and Utility

---

## Challenges and Opportunities

**Ebony Dashiell-Aje, PhD**  
**EuropaBio, BioMarin Pharmaceutical, Inc.**  
**September 21, 2022**

For two decades, increased recognition of the need to generate reliable and valid data that reflects **patient experiences, perspectives, needs, and priorities** to support medical product development.



### Value of data beyond PROs

Importance of outcomes as assessed by various stakeholders (patients, caregivers, clinicians) via various methods to assess clinical benefit

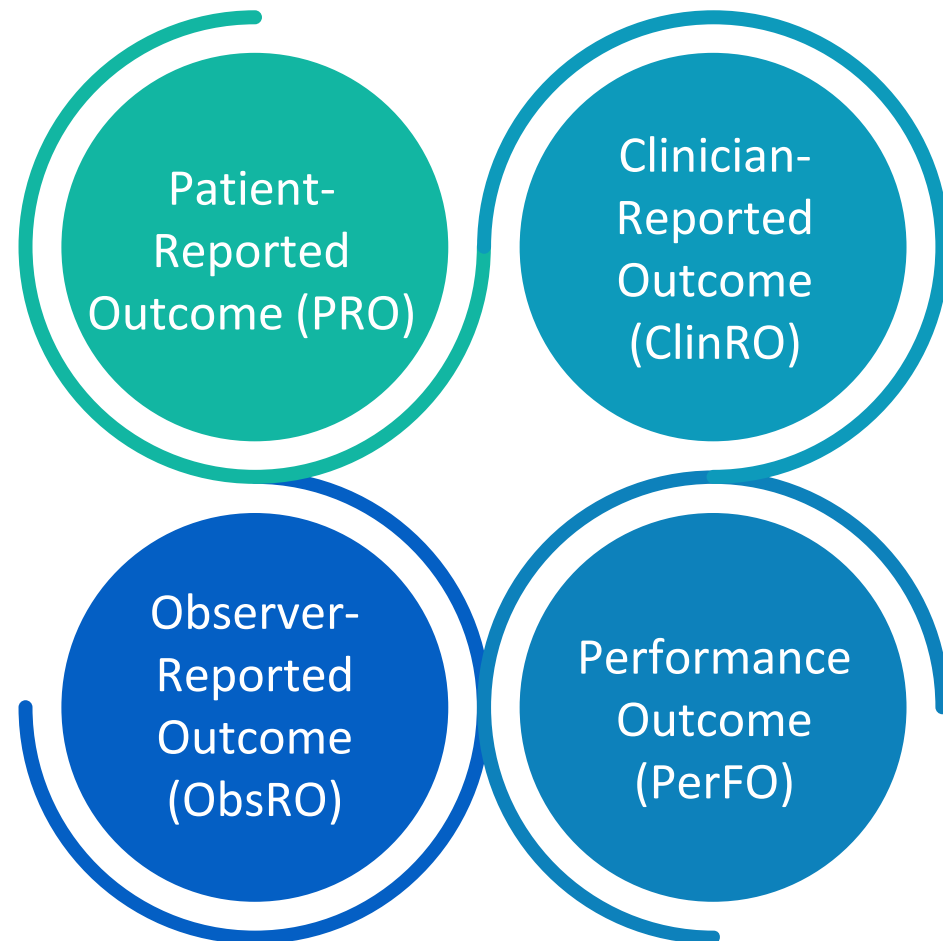
### Global Scope

Increased emphasis on global harmonization to advance COA measurement standards that enable regulatory utility

### Optimization of Initiatives and Partnerships

Emphasis on public-private partnerships to enable collective development of fit-for-purpose COAs that can support regulatory decision-making and product commercialization

COA evidentiary standards are understood. However, **articulation, evaluation, and application** of these standards to support regulatory decisions can be viewed as **incongruent across regulatory bodies**.



### **Content Validity**

The content of a COA reflects concepts that are most meaningful and important to the target population and assess an aspect of health that can be evaluated in a trial

### **Reliability**

The COA can generate consistent and reproducible data over time

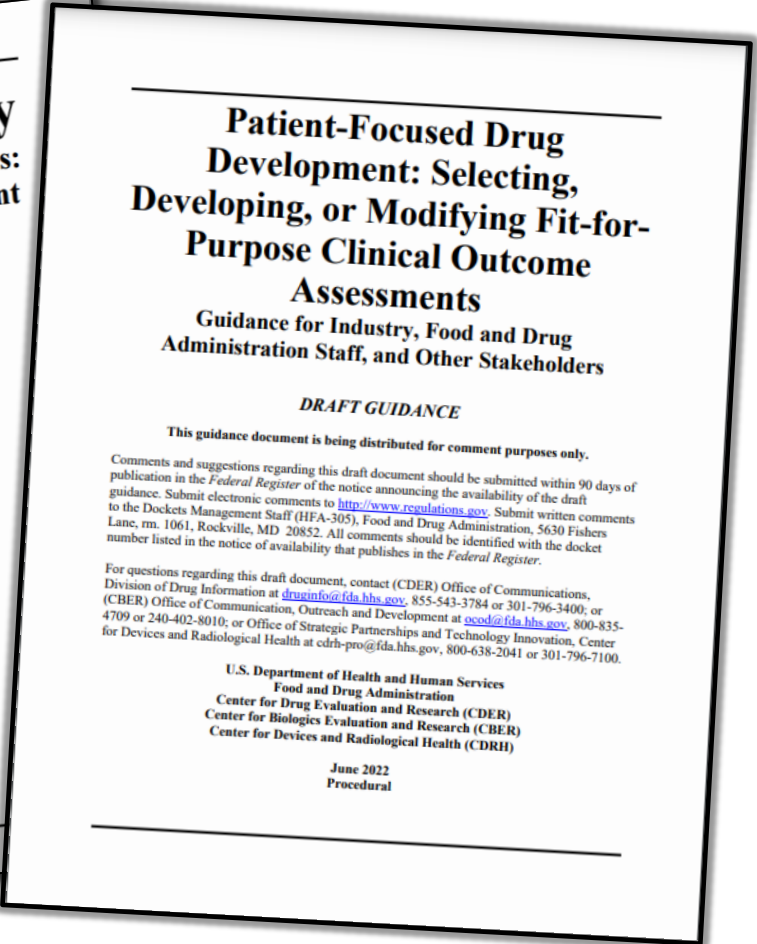
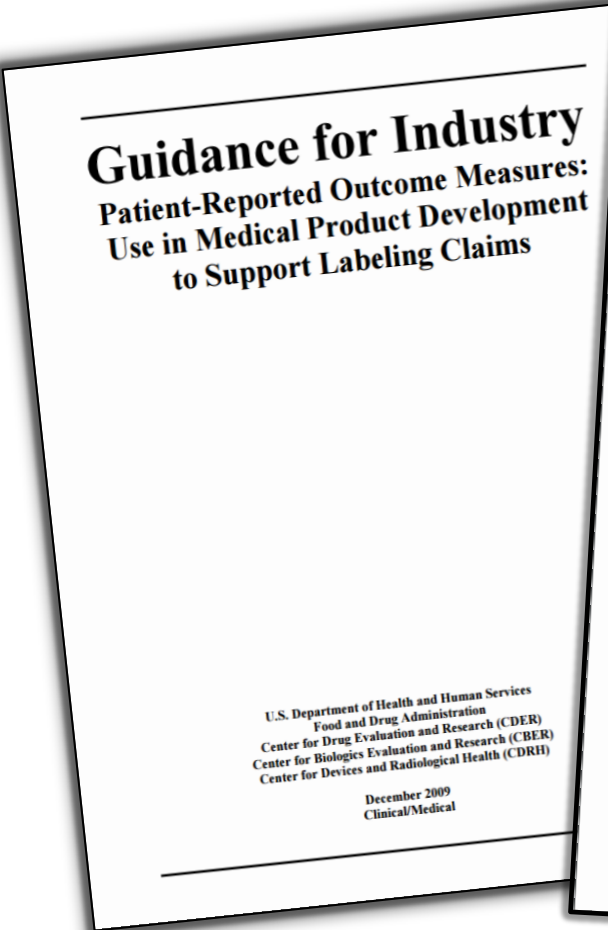
### **Construct Validity**

The COA can measure what it is supposed to measure as demonstrated by reasonable quantitative relations among concepts, items, and scores.

### **Ability to Detect Change**

The COA is sensitive to detect change over time (e.g., improvement) and these changes are interpretable

To date, the FDA PRO Guidance and PFDD Guidance series still serves as the **evidentiary roadmap** for EMA and global regulatory bodies.



Additional considerations from EMA would be helpful to guide sponsors and set realistic expectations around the utility of planned evidence to support approval decisions and labeling claims.

Scientific Advice, Qualification, and multi-stakeholder collaborations encouraged for advancement of COA utility in EMA decision-making but **the pathways to engagement are not always straightforward.**



Early engagement through Scientific Advice critical for alignment on COA measurement strategy



Qualification pathway encouraged and beneficial to facilitate communication and to address measurement challenges



Multi-stakeholder collaboration (e.g., through consortia) is another option toward increasing robustness of COAs

# There is **still room for greater progress** in guiding stakeholders on what constitutes sufficient evidence to enable the use of COAs to support regulatory decision-making and labeling claims

- **Increase transparency on evidence deemed necessary** for adoption of COA data to support regulatory decision-making (especially when applying regulatory flexibility in rare disease drug development) and labeling claims
- **Provide a clear roadmap for timing of engagement and alignment** with EMA on COA measurement strategy during Scientific Advice and Qualification
- **Outline pragmatic approaches** and specific considerations for COA evidence generation, especially in the context of globally harmonized standards
- **Reduce barriers** associated with regulatory-sponsor engagement for Scientific Advice and Qualification (e.g., expertise, cost, time)

# Back-Up

Industry Case Studies

# Case Study #1



## Introduction/ Background

- A recent approach was adopted at Janssen of integrating patient-experience data (PED) into the NDA for esketamine (SPRAVATO®) nasal spray with a newly initiated oral antidepressant (esketaamine + AD) for treatment-resistant depression <sup>1</sup>.
- During the development of esketamine + AD, PED were collected using several patient-reported outcomes (PROs), as well as a patient-preference study assessing the relative importance of benefits and harms that patients allocated to different attributes of treatment <sup>2</sup>. PRO data collection was included in all the phase 3 pivotal clinical trials. Preferences were collected from patients enrolled in phase 3 esketamine trials and from an online panel of primarily ketamine-naive patients.
- The sponsor integrated PED into the esketamine NDA, the FDA advisory committee meeting briefing document, and the Sponsor's presentation.
- The FDA review document included information on the PED <sup>3</sup> and considered the patient perspective when deciding on approval. FDA reviewed data from PRO measures in the clinical trials and feedback from patient advocacy groups and individual testimony <sup>4</sup>.

## Tasks and Actions by Sponsor and HA

### Sponsor:

- Janssen proactively used several methods to collect PED during the drug development of Spravato, including a variety of PROs and a patient-preference study.
- PROs <sup>1</sup>:
  - Evidence supporting the content validity and measurement properties of the PROs was reviewed to assess whether the instruments were fit for purpose in the context of the phase 3 trials. When gaps in the supportive evidence were identified, additional data were generated to support selected PROs for use in the phase 3 trials.
  - Feedback on the proposed PROs was solicited from FDA and EMA during drug development.
  - The FDA's PRO guidance was followed regarding appropriate implementation of PROs in clinical trials.
- Patient Preference Study <sup>1, 2</sup>
  - A discrete-choice survey was conducted amongst trial participants and treatment-naïve panelists to evaluate relative importance of benefits and harms associated with treatment and to quantify the maximum acceptable risk patients would accept for treatments that relieved depression.
  - Planning for the preference study began prior to the start of the phase 3 trials. Development and implementation of the preference study spanned more than 1.5 years.

### Health Authority:

- The PED were included in the esketamine NDA, the FDA briefing information for the Advisory Committee meeting <sup>5</sup>, and the Sponsor's presentation at the Advisory Committee meeting. FDA review of the esketamine NDA included the creation of the patient-experience checklist by FDA and extensive discussion on the PRO and patient preference study.
- FDA's publicly available multifunctional drug review of esketamine highlighted the FDA focus on PED. <sup>3</sup> For the Sponsor, this was one of the first times that FDA provided extensive review of data of an industry-led preference study to support patient acceptance of the benefit risk profile.
- PRO data were assessed by both the FDA and EMA across all the instruments administered to capture depression, function, anxiety and generic health related quality of life. These all contributed to the overall assessment since they consistently showed trends in favor of esketamine <sup>3, 7</sup>.
- Patient preference data contributed to the votes at the FDA Advisory Committee <sup>6</sup>.
- Patient voice concerns were taken into consideration from the open public hearing and the patient representative on the committee, such as the ongoing urgency for additional safe and effective treatments for TRD and the need to consider functional outcome measures for esketamine's effects on TRD. <sup>3</sup>

## Outcome/ Impact (of Agency Interaction)

### Feedback from Agency:

- The FDA reviewed these PED as indicated in the PED checklist and more extensively in other places in the clinical review document <sup>1,3</sup>.
  - The key secondary endpoints based on the SDS and PHQ-9 data could not be formally evaluated for statistical significance or included in the esketamine label. This was because although these PROs were prespecified to be assessed in a hierarchical fashion in the statistical analysis plan, one or more endpoints earlier in this hierarchical order were not statistically significant.
  - The patient-preference study informed the FDA on the unmet medical need:
    - “Overall, these survey results indicate that potential patients with TRD considering esketamine treatment would likely accept the issues with dissociation and waiting time and not driving home in order to obtain clinically significant improvement in their depressive symptoms”.
    - However, “patients may not be as tolerant of serious issues with cognitive-impairment and bladder toxicity (although these issues were described as “permanent” in the survey which would intensify concern)”.
  - Patient voice concerns were taken into consideration from the open public hearing and the patient representative on the committee, such as the ongoing urgency for additional safe and effective treatments for TRD and the need to consider functional outcome measures for esketamine’s effects on TRD. <sup>3</sup>
  - FDA considered the patient perspective when deciding on approval. FDA reviewed data from PRO measures in the clinical trials and feedback from patient advocacy groups and individual testimony <sup>4</sup>.

### Risks/ Challenges

- This experience with esketamine NDA demonstrates the significance of early planning for and integrating PED in drug development.
- The FDA encourages sponsors to discuss patient engagement methods and approaches early in development and often.
- The US FDA developed a Patient Experience Data Checklist, which they include in their Medical Product Reviews. Additionally, sponsors have the opportunity to include the PED Checklist in the submission in the Reviewer’s Guide. Although EMA accepts and supports the inclusion of PROs and patient preference studies in MAAs, there is no EMA definition of PED. An EMA process for acknowledging the inclusion of all types of PED that may have been generated by the applicant throughout the development program is currently not available.

### (Potential) Solutions:

- Development of specific EU regulatory guidance on PED in the MAA, EPAR and product information.
- Develop more timely and efficient mechanisms for discussions with regulators for patient centric approaches throughout development.

## Results/Impact on Development

- The example of esketamine NDA demonstrates the importance of early planning for and integrating patient-experience methods early in drug development, which can help identify the patient-relevant risks and benefits and ultimately benefit patients and clinical program designs.
- The patient-experience data collected by Janssen and its integration into the NDA for esketamine for the treatment of patients with TRD assisted the FDA in its regulatory evaluation and decision-making. Both the FDA and its advisory committee used the patient-preference data as part of their assessment of patient acceptance of the benefit-risk profile of esketamine + AD.
- The FDA’s publicly available clinical review of esketamine + AD highlighted its focus on patient-experience data.

## Key Takeaways

- Patient experience data like PROs and patient preference studies are supportive of the clinical efficacy data.
- Increase transparency on generated patient-experience data for medicinal products registered via EMA.
- Significance of early planning for and integrating patient experience data in drug development.
- Early and repetitive health authority interactions are important but need to be more efficient and aligned with drug development timelines.

## References (accessed 16 Aug 2022)

1. <https://link.springer.com/article/10.1007/s43441-021-00340-6>
2. <https://www.sciencedirect.com/science/article/pii/S0941950020300348>
3. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2019/211243Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000MedR.pdf)
4. <https://www.nejm.org/doi/10.1056/NEJMp1903305>
5. <https://www.fda.gov/media/124158/download> (page 297 of 355)
6. <https://www.fda.gov/advisory-committees/february-12-2019-joint-meeting-psychopharmacologic-drugs-advisory-committee-pdac-and-drug-safety-and#event-materials>
7. <https://www.ema.europa.eu/en/medicines/human/EPAR/spravato>

# Case Study #2

## **Introduction/ Background**

- This case study demonstrates the value of integrating the patient and caregiver voice into the decision-making process in all phases of medical product development. The early and systematic partnerships between the spinal muscular atrophy (SMA) community and Roche helped shape the company's clinical development programme in SMA and was central to ensuring faster and broader patient access and improving outcomes. Furthermore, through work with patients and COA measurement experts, a new scale was developed, validated and used in the regulatory submission to solve for the challenge that there were no well-defined endpoints in SMA.
- SMA is a genetic disease affecting the central nervous system, peripheral nervous system, and voluntary muscle movement (skeletal muscle).

## **Actions by Sponsor to develop a new Clinical Outcome Assessment**

- The sponsor partnered with the SMA community throughout development. In this section we would like to share specifically the development of a novel Clinical Outcome Assessment as an outcome of these partnerships.
- The sponsor conducted patient and caregiver interviews to better understand the disease burden in Type 2 and non-ambulant Type 3 SMA patients. Through in-depth qualitative concept elicitation and cognitive interviews, we identified maintaining/improving independence related to the level of assistance needed for activities of daily living as a key outcome relevant to patients with Types 2 and non-ambulant Type 3 SMA. Since existing patient- and observer-reported outcome measures used in this population do not capture this concept of interest, we developed the SMA Independence Scale - Upper Limb Module (SMAIS-ULM) for the SMA community with COA measurement experts. Psychometric evaluation of the longitudinal and cross-sectional measurement properties was conducted using quantitative survey data and clinical trial data from a phase 3, double-blind, randomized, placebo-controlled trial evaluating risdiplam in Type 2 and non-ambulant Type 3 SMA. As FDA emphasized in its recent draft PFDD 3 Guidance, sharing of COAs between sponsors and researchers will help to promote efficiency and maximize the returns on the efforts made by patients in developing these tools. Therefore, following updates to the scale and further cross-sectional validation, we have made the SMAIS-ULM available to the public via the ePROVIDE platform. As such it can be used in clinical practice and future trials to monitor patients/assess benefit, and is already being used globally, including in large registries.

### **Outcome/ Impact on Health Authority review process and decision**

- Patient Advocacy Groups advanced the sponsor's understanding regarding the existing unmet need, and what treatment effects were most relevant. In addition, they were also key in the HA review process. Members of the SMA Foundation were invited to regulatory meetings to provide the HA with insights from people living with SMA directly. In addition, patient views, published data from PAG-led surveys (e.g. Voice of the Patient report, EUPESMA) alongside the patient-reported outcome data (SMAIS) from clinical trials, were included in regulatory applications to capture the unmet need and real-life value of SMA treatments. This supported HAs in their review, as evidenced in the mention of the SMAIS score showing evidence of the benefit of the medicines in the EPAR (Risdiplam Public Assessment report, EMA/216061/2021).

### **Results/Impact on Development program**

- The sponsor was able to design clinical trials that reflected the needs of the patient community (e.g., included broader age range, severely impacted patients [e.g., with scoliosis, contractures etc.]). Furthermore, the sponsor was able to include endpoints that capture what matters to patients (and provided in turn a better understanding on the medicine's profile).
- In addition, better understanding of the disease also allowed for requesting and granting of special regulatory procedures for rare disease and areas of unmet need, such as for example Priority Medicine (PRIME) designation, Orphan drug designation, and Fast track granted in the US.

### **Key questions for the workshop**

- Even though the COA was reported in the EPAR, it remains unclear the extent to which HAs base their regulatory decisions on Patient Experience Data. We welcome more clarity and transparency on the impact of this data.
- More clarity is also needed in terms of what PED constitutes (e.g. beyond PROs), sponsors welcome HAs to expand the scope of PED to also include insights collected from unstructured interactions (e.g. ad boards, consultations etc.)
- It is essential that Health Technology Assessment Bodies also consider PEDs and that there is alignment between HTAs and Health Authorities on the use of patient-led insights for regulatory and access decision making.

# Case Study #3

### **Case Example:**

## **Early Incorporation of Patient Input into Clinical Outcome Assessment (COA) Strategy: End-of-Phase 1 Stakeholder Alignment on Key Patient-Reported Outcomes (PRO)**

### **Introduction/ Background**

- A pharmaceutical company is in early-stage development of an oncology product.
- Product team has developed a patient-focused strategy to inform drug development and regulatory decision-making.

### **Tasks and Actions by Sponsor and HA**

- During Phase 1 clinical development, company conducts patient advisory boards and concept elicitation interviews with patients
- As the product advances through Phase 1 studies, company initiates planning of its COA strategy for Phase 2 and 3 trials using the information obtained from direct patient engagement
- To optimize capture of patient experience data and expand the data to label, company includes an approach utilizing electronic PRO with a wearable device into the COA strategy



## Results/Impact on Development

- Through early patient interactions, company elicits patient perspectives on the severity of the condition, most bothersome symptoms, the disease's impact on daily living, and unmet medical need.
- Patient input helps validate conceptual model for disease of interest and inform the identification/selection of patient-relevant concepts and outcomes.
- Patients provide input into the schedule of assessments, use of the COA instrument, use of wearable device, and perspectives on potential burden of incorporating a particular COA instrument into the trial (e.g., number of assessments, electronic vs. paper instrument, home collection vs. onsite collection).
- Patient input is critical to informing the COA strategy and overall endpoint selection.
- Patient input can inform preparations for regulatory meetings and in addition to literature, the perspectives may help supplement the rationale for validating the selection of certain concepts or COA instruments and use of innovative approaches (e.g. wearables).
- During formal regulatory interactions throughout the drug development process, health authorities may inquire about the selection of trial endpoints, COA strategy, or PROs utilized. In response, the company can present the patient-centric approach and feedback collected as rationale for including specific metrics in registrational trials.

## Key Takeaways

- Early patient engagement is critical for shaping a development program across several areas.
- While the patient perspective not only drives the COA strategy, it can also inform other aspects of the development program, including clinical trial considerations and digital health integrations.
- Insights gained from patients can provide support and rationale for clinical endpoints, which can be shared with regulators as part of the strategy for the registrational clinical trial and supporting studies for the marketing application.

# Case Study #4

## Introduction/ Background

- This case example highlights how patient experience data (PED) can be used to inform both endpoint development and regulatory decision-making to communicate treatment benefits on symptoms important to patients.
- Irritable bowel syndrome with constipation (IBS-C) is a chronic gastrointestinal disorder characterized by abdominal pain and constipation, with additional symptoms of straining, abdominal bloating, and abdominal discomfort commonly experienced by patients.

## Tasks and Actions by Sponsor and HA

- Extensive qualitative and quantitative research was conducted by AbbVie, in partnership with Ironwood Pharmaceuticals, to generate robust evidence to support the PRO items included in the pivotal trials for linaclotide to measure key signs and symptoms of IBS-C important to patients for a treatment to improve, inclusive of abdominal symptoms of bloating, pain, and discomfort.
  - Literature reviews and qualitative interviews with IBS-C patients were completed to inform selection, development, and implementation of PROs in the linaclotide pivotal trials.
  - Psychometric analyses utilizing clinical trial data were completed to generate quantitative evidence to support the measurement properties of the PROs implemented in the trials.
  - All primary and secondary endpoints were PROs.
- The Sponsor also engaged with the FDA's Division of Gastroenterology and Division of Clinical Outcome Assessment early and often throughout the linaclotide development program, beginning as early as Phase 2, to confirm alignment with the proposed PRO measurement strategy, inclusive of:
  - The concepts identified for measurement,
  - The PRO items used to measure the concepts, and
  - Endpoints defined based on the PROs.
- In parallel to the Sponsor's engagement with regulatory authorities, the Sponsor also worked collaboratively with key stakeholders, including other industry sponsors, clinical key opinion leaders, IBS-C patients, advocacy organizations, measurement experts, and the FDA, as a co-chair of the Critical Path Institute's IBS Working Group to develop a new PRO instrument for use as a primary endpoint in IBS-C clinical trials that was in line with FDA's PRO guidance and inclusive of abdominal symptoms important to patients (Diary for Irritable Bowel Syndrome Symptoms – Constipation [DIBSS-C]).

## Outcome/ Impact (of Agency Interaction)

- The same evidence package was submitted with the linaclotide MAA to the EMA and NDA to the FDA to support the PRO measures included in the pivotal trials, highlighting the salience of the concepts identified as important to IBS-C patients and the reliability and validity of the PRO items.
- There was some variability in the decisions:
  - EMA: In addition to the primary endpoints of IBS degree of relief responder and abdominal pain/discomfort responder, all key secondary endpoints (inclusive of bloating, complete spontaneous bowel movement [CSBM] frequency, straining, and stool consistency) as well as quality of life were included in the SmPC for linaclotide.
  - FDA: The primary endpoints of combined abdominal pain and CSBM responders were included along with key secondary endpoints of abdominal pain, CSBM frequency, stool consistency, and straining, in the initial labeling for linaclotide.
- As recommended and agreed to with the FDA following initial approval, additional evidence was generated through the IBS Working Group from (1) qualitative research with patients on the importance of abdominal symptoms and (2) quantitative analyses from trial data to support use of an abdominal score inclusive of pain, discomfort, and bloating for evaluating treatment benefit in IBS-C patients.
- The DIBSS-C was included by the Sponsor in a Phase 3b trial of linaclotide in IBS-C as a measure of abdominal symptom severity.
- Data generated from the Phase 3b trial provided confirmatory evidence supporting the psychometric properties of the abdominal symptom items and abdominal score (comprised of 3 items of bloating, pain, and discomfort) and thresholds for clinically meaningful change in the abdominal score to support primary and key secondary endpoints in the trial.

## Results/Impact on Development

- Confirmatory psychometric data for the DIBSS-C and proposed thresholds for clinically meaningful change for the abdominal score were submitted along with the Phase 3b clinical trial results in an sNDA to the FDA.
  - The Sponsor engaged with the FDA to align on the appropriate threshold for clinically meaningful change on the abdominal score.
  - Following alignment, the Agency agreed to update the linaclotide label to include the abdominal score.
- The updated US label for linaclotide now reflects additional benefits on key symptoms of abdominal bloating and discomfort, previously only communicated in the EMA SmPC.

## Key Takeaways

- The success of inclusion of PED in the linaclotide label highlights the importance of investment in scientifically rigorous research to identify and measure what matters to patients, early and often interactions with regulatory authorities, and multi-stakeholder engagement to develop a successful measurement strategy.
  - Numerous interactions, specifically with the FDA, were needed to gain alignment on concepts important from the patient perspective and the evidence needed to support their inclusion in labeling.
  - Extensive PED generated through qualitative interviews highlighted the ways in which patients described their symptoms, including what is clinically meaningful, and the importance of improving them in the context of their condition to support the linaclotide PRO strategy.
  - Multistakeholder collaboration including other sponsors, patients, measurement experts and FDA was critical in enabling the incorporation of the patient's voice in IBS drug development and product labeling.
- Looking forward, there is a need for harmonization across regulatory authorities to create efficiencies in research conducted to advance the incorporation of the patient's voice in drug development, greater predictability in guidance on the use and submission of PED to support regulatory decision-making, and an awareness of key divergences in evidentiary needs across regulatory agencies.